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Barriers that prevent initial prescription of hydroxyurea in sickle cell disease

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Introduction

Sickle cell disease (SCD) is one of the most common inherited red blood cell disorders, affecting millions of people worldwide. According to CDC, SCD affects approximately 100,000 Americans and is most prominent in people with ancestry from sub-Saharan Africa, Spanish-speaking regions in the Western Hemisphere (South America, the Caribbean, and Central America), Saudi Arabia, India, and Mediterranean countries such as Turkey, Greece, and Italy.[1] 1 out of every 365 black or African-American and 1 out of every 16,300 Hispanic-American children are born with SCD.[1] Approximately 6,000 Latin Americans are born with SCD annually in both US and Latin American countries. However, of all the Latin Americans countries, only Brazil and Costa Rica have new born screening for SCD and have treatments to reduce SCD related morbidity and mortality in children.[3]

SCD is an autosomal recessive disorder, resulting in a sickle shaped red blood cell (RBC) due to the presence of an abnormal hemoglobin molecule. The abnormality of the RBC causes decreased oxygen carrying capacity, impaired blood flow through microcirculation and tissue ischemia when compared to a normal RBC. The most common genotypes of SCD are HbSS, HgSC and HbS beta thalassemia. HbSS variant also called sickle cell anemia presents with most serve form of the disease. HbSC variant is a less severe version of HbSS. HgS beta thalassemia variant presents with characteristics of both SCD and beta thalassemia. Sickle cell trait is a clinically benign variant, where the person is a carrier of the sickle hemoglobin gene and can pass on the gene to the future generations.[2]

SCD has variable clinical presentation and severity of symptoms due to its many variants. Some of the symptoms and complications associated with SCD are chronic hemolytic anemia, acute chest syndrome, deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, splenic

sequestration, infections, leg ulcers and pain. Sickle cell crisis is an exacerbation of SCD precipitated by infection, dehydration, cold, acidosis, hypoxia and pregnancy.

Pain in SCD can be both acute and chronic. Patients often present with recurrent acute painful episodes known as vaso-occlusive crisis. This occurs due to the clumping of the RBCs causing acute pain in hands, feet, severe bone pain resulting in avascular necrosis, ischemia and infarction to multiple organ systems.[1,2] A large number of patients can also present with chronic pain syndrome due to chronic skin ulcers, bone and joint damage. Pain is the leading cause of hospitalizations and emergency department visits in SCD. [2]

Diagnosis of SCD in the United States is age dependent and is made via prenatal screening for expecting couples at risk, new born screening for early detection of SCD in infants, and laboratory screening methods for undiagnosed children and adults.[2] Current management of SCD includes routine health management to decrease complications, preventive visits for infections, blood transfusions and pain management. Hydroxyurea (HU) and L-glutamate are United States Food and Drug Administration approved treatment for painful vaso-occlusive episodes and Hematopoietic stem cell transplantation is the only cure available.[2]

HU has been in use for decades to treat SCD. It is a myelosuppressive drug that works by decreasing vaso-occlusive episodes, increasing production of the fetal hemoglobin and decreasing the production of the sickle adult hemoglobin. HU reduces complications, morbidity and mortality in people with SCD by reducing the number of vaso-occlusive episodes, acute chest syndrome episodes, number of hospitalizations and the number of transfusions.[2] Despite the evidence to support the safety and efficacy of HU, its use in clinical practice is suboptimal. In this review, barriers that prevent the initial prescription of hydroxyurea are examined. Addressing these barriers could aid in optimal utilization of HU in treating and preventing

complications of SCD. Preventing complications will not only help the physical and psychological well-being of patients but may also result in reducing healthcare related costs. The objectives of this review are to: 1) examine barriers related to low provider prescription rates of HU; and 2) examine barriers related to patient perception of HU.

Methods

Information for this paper was gathered from a literature search conducted using PubMed database, Google Scholar, United States Centers for Disease Control and Prevention (CDC) and UpToDate websites. Key words used for the search included “barriers to hydroxyurea in sickle cell disease", "hydroxyurea barriers sickle cell disease", "hydroxyurea sickle cell disease", "Provider barriers in sickle cell disease", "Hydroxyurea adherence and barriers”.

CDC and UpToDate websites were utilized to cross-reference background of the disease including epidemiology, diagnostics, treatments and statistical evidence presented in the articles.

Background

Hydroxyurea

Many studies have been successful at providing the evidence to support the efficacy of HU in children and adults with HbSS [5,6] HU can be prescribed for infants younger than 9 months and adults for symptomatic disease. For infants older than 9 months, children and adolescents, HU is recommended regardless of disease severity.[2]

HU is effective in preventing pain and acute chest syndrome and reducing transfusions and hospitalizations in SCD. [8] In a prospective longitudinal follow-up study, after initiation of HU in children aged 1, no pain episodes requiring medical attention were observed. Additionally, no complicated acute chest syndromes or overt strokes were noted.[8]

By reducing the frequency of complications, HU can limit healthcare related costs in SCD. In a retrospective economic evaluation study done by Winfred et al., HU demonstrated clinical benefits for infants and toddlers with SCD by reducing the frequency of painful episodes, dactylitis, acute chest syndrome episodes, fewer hospitalizations and lesser transfusions. HU was associated with lower healthcare expenses when compared to a placebo by 21%.[5] The study concluded that HU treatment was associated with substantial healthcare savings and that they would become more prominent in patients older than three years of age due to occurrence of increased frequency of hospitalizations in older children. They suggested HU treatment to all children at a young age due to its efficacy, limited toxicity and its relatively easy administration.[5]

Other medication options, advances in treatment and research

There are other medications and treatment options being studied for SCD. Butyrate, decitabine and 5-azacytidine are other medications used in SCD which work by increasing the fetal hemoglobin production and decreasing the production of the sickle cells. Crizanlizumab and Poloxamer 188 are medications that prevent cell-cell adhesions and improve flow dynamics in SCD respectively. Crizanlizumab is a monoclonal antibody and is given intravenously.[4] Voxelotor (GBT-440) is new medication that works by binding to the sickle hemoglobin molecule, increases its affinity to oxygen and prevent damage to the RBC.[4] Further studies are needed to learn more about these medications and to understand their risks and benefits in treating SCD.

Bone marrow transplantation is the only cure available for SCD. It is reserved for selective candidates and has considerable risk of morbidity associated with it.[6] Preschool age is the ideal age and siblings are optimal donors, both of which can limit its use.[2] There is little data

on unrelated donors for transplant.[9] There is also lack of data to support the use of bone marrow treatment over HU.[2]

Hence, gene therapy is being explored as another curative option. Different gene therapy options are being developed to identify mutated SCD deoxyribonucleic acid (DNA) sequences, cleave the mutations and replace or modify these altered DNA sequences with properly sequenced DNA.[4]

Although new medications under investigation and gene therapy are bringing hope to finding new treatment modalities in SCD, additional clinical trials are needed to study the efficacy and side effect profile of these new treatments. Until then, HU should be utilized in treating and preventing complications of SCD.

Provider related barriers

In both pediatric and adult studies looking at the use of HU in SCD, the most common provider related barrier noted was patient compliance, meaning providers did not offer HU to patients as they thought patients would not be compliant with taking the drug or with follow up labs to monitor HU levels.[9]

A survey was done by Lanzkron et al. to look at the prescription patterns of HU in providers who treated SCD patients both in clinics and hospitals. Adherence to National Heart, Lung and Blood Institute (NHLBI) guidelines on recommendations of HU for sickle cell disease was used as a way to measure and identify barriers to HU prescription. In this survey, 81% providers reported they were familiar with the guidelines and 76% agreed with the guidelines however only 45% prescribed HU to every eligible SCD patient.[11] The most common reasons providers reported for not initiating HU treatment were: patient noncompliance in getting the required blood tests, patient's inability to use the appropriate contraception, and patient

noncompliance with taking HU.[11] Some of the other concerns providers reported for under prescribing HU were patient's age, patient's knowledge of HU and its side effects, and providers lack of time and resources.[11] Some of these concerns can be reduced by counseling and educating patients on HU therapy.

HU therapy counseling is done to help patients understand the benefits and the risks associated with HU therapy in SCD. Low adherence to HU therapy counseling by providers during initial prescription of HU is another provider related barrier. National guidelines on SCD recommends providers counsel all patients and families about HU therapy. [7] In a study conducted by Cabana et al. involving Pacific Sickle Cell Regional Collaborative (PSCRC) composed of 15 clinical sites, an 8-page questionnaire was used to identify the barriers that resulted in low adherence to HU therapy counseling in providers.

Most providers from the above study were familiar with the guideline recommendations (93%). However, almost half of the providers (49%) reported lack of self-efficacy as the most common barrier.[7] 30% reported lacking self-efficacy in recognizing which patients may benefit from HU, 28% in prescribing the appropriate dose, 28% in recognizing the side effects, and 37% reported lacking self-efficacy in discussing the risk of HU therapy with patients and families. 44% provides expressed concerns on patients' ability to comply with HU regimen. Some of the other barriers reported were lack of equipment, space, time, educational materials, support staff and reimbursement.[7]

Patient related barriers

Patient related barriers of HU include fear of cancer (51%), fear of side effects (62%), refusal to take medication (49%), refusal to comply with the required laboratory monitoring (28%), and rejection of HU because they didn't believe in its efficacy (17%).[10] There is a US boxed warning

stating HU as a carcinogen with advice on sun protection and patient monitoring for malignancies. However, there is not enough data to support carcinogenesis of HU in SCD.[9] Obtaining refills of the medication and clinic follow up visits were identified as other barriers.[9]

Families of children with SCD were more likely to comply with HU treatment, laboratory monitoring and frequent follow ups if they believed the treatment would be beneficial.[6]

Formulation barrier could be another patient related barrier when initiating HU treatment in infants and children. Parents can be unaware of the availability of liquid formulations of HU and can shy away from the medication.

A liquid formulation of HU made by the pharmacy is available for infants and young children who cannot tolerate swallowing capsules.[6] The liquid formulation is prepared from HU capsule contents or through dissolving bulk HU powder in water vigorously. A sweetener can be added to make the preparation more palatable for infants and children.[6] HU dose is started at a low dose and incrementally increased to the maximum tolerated dose. Fine tuning of the dose to the maximum tolerated dose can be done easily by the liquid formulations of HU.[6]

Discussion

HU has been the standard treatment for SCD since the late 1980's and can be prescribed for a varied age group from infants to adults in treating SCD.[4]

Initiation of HU in 1-year old children helped eliminate certain complications such as painful episodes requiring medical attention, complicated acute chest syndrome and overt strokes in a prospective follow up study done by Thomas et al.[8]

HU therapy can lower healthcare expenses by 21% when compared to a placebo.[5] As HU can reduce complications and hospitalizations, it can decrease the burden of healthcare costs, which would help both the patients and the health care system in healthcare savings. These

savings would increase, as Winfred et al. concluded, as patients get older.[5] All these reasons make HU an optimal therapy for current management of SCD and utilizing it to its full potential will help reduce complications and healthcare costs associated with SCD.

Additional treatments under investigation are butyrate, decitabine, and 5-azacytidine, but more studies are needed to show safety and efficacy of these medications.[4] Crizanlizumab is a monoclonal antibody that prevents cell-cell adhesions in SCD and is given intravenously every month.[4] FDA recently gave Crizanlizumab a breakthrough therapy designation.[12] However, intravenous administration can be a disadvantage for its use, especially as more feasible medications exist. Voxelotor, another medication seeking FDA approval, binds the sickle hemoglobin molecule, prevents damage to the RBC and increases affinity to oxygen.[4] Voxelotor showed promise in phase 3 trials with 7 participants, where it reduced hospital admission for vaso-occlusive episode by 60% and decreased frequency of transfusions by 50%.[4] Further studies with larger number of participants are necessary to establish its efficacy.[4]

Different gene therapy options being developed offer hope in curing SCD. These new treatments and research in gene therapy are encouraging to SCD patients and provide more treatment options. While these novel treatments are under study, HU can be used for its established efficacy and low toxicity level.

To understand more about HU's inadequate initial prescription rates, provider related barriers were explored. The most common provider barriers noted were patient compliance with either taking HU or with follow up and monitoring required for the medication. Providers did not think that patients would be compliant with a medication that could potentially decrease morbidity and mortality in SCD. This might be true for some patients, but it should not create a bias against all other eligible patients. This provider bias against SCD patients dampens the

effectiveness and health benefits HU could provide. This is a major barrier to the initial prescription of HU and the first step in addressing this barrier is to make the providers recognize and realize this bias. Bringing awareness to providers concerns can help develop strategies to address the barrier.

81% providers were familiar with the guidelines on prescription of HU and 76% of them agreed with the guidelines, only 45% prescribed it to eligible patients.[11] This discrepancy between knowing and agreeing with the guidelines and prescribing HU poses a significant challenge in increasing the prescription rates of HU. Even if providers think patients are not going to be compliant with the medication, they should still offer the medication while finding ways to increase the compliance by educating the patients and addressing patient identified barriers. Patient non-compliance can also be due to access to a local pharmacy, liquid formulation access, side effects or fear of carcinogenesis of HU. These are the concerns that providers should address through HU counseling. However, HU counseling itself is another provider related barrier due to low adherence to the recommended guidelines.

All providers are required to educate and counsel all eligible SCD patients on HU therapy at initial prescription of HU therapy according to the national guidelines. Even though 93% of the providers were familiar with these guidelines, 49% of them did not adhere to the guideline due to lack of self-efficacy. Almost half of the clinicians lacked confidence in their ability to perform HU counseling, 30% lacked self-efficacy in recognizing patients that could benefit from HU therapy, 28% did not understand the appropriate dose prescription, 37% were not confident in their ability to discuss the risks and side effects associated with HU, and 44% providers had concerns with patient's compliance with the therapy.[7] Lack of self-efficacy in providers is a barrier that can be addressed through resources, learning, and practice.

The lack of knowledge or confidence in providers should not reduce prescription of a drug that is extremely beneficial. Patient compliance was brought up again for counselling on HU therapy. How can clinicians expect patients to be compliant on a therapy if the patients do not receive proper counseling? Education should be provided to clinicians on how to perform appropriate HU therapy counselling and the importance of it in increasing the rates of HU prescription for both the welfare of the patients and lowering health care related costs. There is a lack of educational resources for providers to prevent these barriers and a need for more resources to be developed.

There is minimal data on patient related barriers compared to provider related barriers.[9] Patient related barriers are more geared around not having sufficient knowledge about HU efficacy, its side effects and toxicities. Fear of cancer (51%) and side effects (62%) is a large part of patient related barriers. Some of HU side effects include cytopenia's, hyperpigmentation to nails or skin, abnormal semen and spermatogenesis, teratogenic effect in females, and increased risk of developing a malignancy.[9] Cytopenia's normally reverse after the cessation of HU and low doses of HU can be given to people who experience the cytopenia's. The data is insufficient to conclude any relation between abnormal semen and spermatogenesis, and teratogenic effect in females with HU.[9] Similarly, there is not enough evidence to support any relation between HU use in SCD and the increased risk of malignancy.[9] More studies looking at the side effects and toxicities of HU use are needed to support or oppose these claims. Patients who are afraid to start the HU therapy due to these reasons should be given information about the benefits and the risks involved in starting HU therapy and should then be allowed to make an informed decision weighing out the benefits against the risks.

Some of the other barriers identified were obtaining refills to the medication, coming to clinic for follow up visits, and formulation barriers. Parents of SCD children with formulation barrier can opt for the liquid formulation option which is easy to administer and obtain from the pharmacy.

SCD is a chronic disease and starting HU therapy needs certain amount of monitoring and follow up to ensure the safety and the efficacy of the drug. Patients might be more susceptible to monitoring and follow up if they benefit from the drug. HU therapy benefits can be shared with the patients during follow up to increase compliance. Visualization of peripheral blood smear with fewer sickle cell forms can be used to demonstrate the benefits of HU to patients.[6] Peripheral blood smears of several unidentified patients before and after HU therapy can be shown to patients and families to show the efficacy of HU therapy.[6]

Conclusion

Upon examining both the provider and patient related barriers for the initiation of HU therapy, it can be concluded that educational resources about HU therapy can benefit both providers and patients. It should be every providers duty to offer appropriate HU therapy for all eligible SCD patients, regardless of the patient compliance with the medication. If patient compliance is a concern, then measures should be taken to increase compliance by counselling patients on HU's mechanism of action, benefits and risks. Visualization of peripheral blood smear before and after HU therapy and laboratory results can be used to illustrate the benefit of HU therapy at follow-up appointments.[6] Providers can educate patients that blood cells are produced every day in the body so HU should be taken daily for favorable outcome. They can advise patients to use medication score cards, monthly calendar mark offs, and pill containers to remember to take the medication daily.[6]

HU counselling is key in eliminating some of the patient related barriers to HU therapy, hence it is essential to overcome the barrier to low adherence to HU therapy counseling in providers. Emphasizing the importance of HU therapy counseling and sharing adherence statistics with providers can be a first step in addressing this barrier. Many studies have been done to identify the barriers that prevent prescription of HU in SCD, however most of these studies fail to develop solutions to prevent these barriers. Additional strategies or resources should be developed to address provider barriers and more data is needed to learn about the patient barriers.

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